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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/927,395	LIVSHITS ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 8-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 8-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152) .
6) ☐ Other: .

DETAILED ACTION

Claims 1-5 and 8-20 are now at issue and are present for examination.

Applicants' amendments and arguments filed on 3-24-03, paper No.8, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

Claims 3, 8 and 16 are objected to because of the following informalities: Claims 3, 8 and 16 do not recite the biological name "Escherichia" in italics. It is customary in the art to recite biological names in italics. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 15 and claims 16-20 which depend therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 15 recites the phrase "under stringent conditions". A perusal of the specification provides a definition which is very vague or incomplete or at best exemplary. Contrary to applicant's argument, from the above definition for stringent conditions those skilled in the art cannot readily determine those conditions. Therefore the use of the above phrase renders the claim indefinite as used in the context of the above claim. Applicants argue that claim 15 has been amended such that the phrase "under

stringent conditions" is defined as conditions under which a sequence which is > 70% identical to nucleotides 557-1171 of SEQ ID NO:1 will hybridize. However as amended no such definition is recited as "under stringent conditions" is not linked to the >70% homology limitation. In order to take advantage of the exemplary definition provided in the specification for support and to clearly define the phrase "stringent conditions", Examiner suggests amending the claim as follows, "An isolated DNA sequence that hybridizes to nucleotides 557 to 1171 of SEQ ID NO:1, under hybridization conditions in which polynucleotides that are at least 70% identical to nucleotides 557 to 1171 of SEQ ID NO:1 would hybridize to nucleotides 557 to 1171 of SEQ ID NO:1, wherein said DNA encodes....".

In response to the previous rejection of claim 2 for the same reason as above, applicants have amended the claim by deleting such language. Therefore Examiner has withdrawn the rejection of claim 2 under 35 U.S.C. § 112, 2nd paragraph. However such a rejection is now reinstated for claim 15.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DNA with SEQ ID NO:1 or nucleotides 557 to 1171 of SEQ ID NO:1, encoding polypeptide with amino acid sequence of SEQ ID NO:2 which renders the cells in which the DNA is expressed, homoserine resistant, does not reasonably provide enablement for any DNA which hybridizes under stringent conditions to nucleotides 557-1171 of SEQ IDNO:1

and is at least 70% homologous to nucleotides 557 to 1171 of SEQ ID NO:1 and encodes a protein having an activity of rendering a bacterium homoserine resistant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 15-20 are so broad as to encompass any DNA which is a variant, mutant or a recombinant of nucleotides 557-1171 of SEQ ID NO:1 with at least 70% identity thereto and encoding a protein which renders a bacterium homoserine resistant from any or all sources and vectors and host cells (*E.coli*) comprising such DNAs. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of DNA sequences that are broadly encompassed by the claims.

Applicants propose to use the above polynucleotides for recombinant process of production of amino acids. Since the nucleotide sequence determines the type of protein and the ultimate function of the encoded protein and since the predictability of which changes in the nucleotide sequence can be tolerated and still obtain a protein having the desired activity, requires a knowledge of and guidance with regard to which amino acids can be altered and w cannot be altered and a detailed knowledge of the ways in which the encoded protein struct

relates to its function, changing the nucleotide sequences as proposed by the applicants and/or addition of substantial amount of additional nucleotide sequence unrelated to the nucleic acid sequence of SEQ ID NO:1 may not lead to desired function of the polynucleotides. This is because the changes suggested by the applicants will result in an enormous number of nucleotide sequences that may or may not encode the polypeptide which renders the cells resistant to homoserine. It would require undue experimentation of the skilled artisan to make and use the claimed polynucleotides as claimed. The specification is limited to teaching use of SEQ ID NO: 1 and nucleotides 557 to 1171 of SEQ ID NO:1 for encoding a protein that renders a bacterium homoserine resistant but provides no guidance with regard to the making of variant and mutant polynucleotides or with regard to other uses of such polynucleotides. In view of the great breadth of the claim, amount of experimentation required to make the claimed polynucleotides, the lack of guidance, working examples, and unpredictability of the art in predicting function from an encoded polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polynucleotides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or modifications of nucleotides, as encompassed by the instant claims, and the base changes within a nucleic acid's sequence can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to

modification for a given DNA to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any DNA which is a variant/mutant or having 70% homology to nucleotides 557-1171 of SEQ ID NO:1 and encoding a protein which imparts homoserine resistance to a bacterium because the specification does not establish: (A) regions of the DNA sequence which may be modified without effecting the above mentioned activity/utility; (B) the general tolerance of homoserine resistance imparting DNA sequence to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any nucleotide sequence with an expectation of obtaining the desired biological function and utility; (D)a specific hybridization condition and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any or all DNA which are at least 70% homologous to and hybridizes to SEQ ID NO:1 or nucleotides 557-1171 of SEQ ID NO:1 under "stringent conditions" and encoding a protein which imparts homoserine resistance to a bacterium. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of DNAs having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action and rejection of claim 2 under 35 U.S.C. § 112, 1st paragraph, applicants argue that claim 15 is enabled. Applicants submit that provided with nucleotide sequence in SEQ ID NO:1 and the tools necessary to hybridize one DNA to another DNA and determine whether it has necessary homology and activity is within the well-described knowledge available in the art and in support of that applicants submit specific pages taken from a laboratory manual. Applicants also argue that homology searches can be done using the BLAST and FASTA search engines. This is not persuasive to overcome the above rejection because while above methods are well known to the skilled artisan, producing and using polynucleotides as claimed by applicants requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the DNA sequence which may be modified without effecting the above mentioned activity/utility; (B) the general tolerance of homoserine resistance imparting DNA sequence to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any nucleotide sequence with an expectation of obtaining the desired biological function and utility; (D) specific high-stringency hybridization conditions and (E) the specification provides insufficient guidance as to which of the essentially infinite

possible choices is likely to be successful. Therefore the above rejection is maintained for claims 15-20.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5 and 8-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. application/Publication No.09/847,392/20020102670 A1. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim, because the examined claim is either anticipated by, or would have been obvious over the reference claim. See, e.g., *In re Berg*, 140 F.3d 1428,46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi* 759 F.2d 887,225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1-5, 8-20 of the instant application and claims 1-5 of the reference application are both directed to polynucleotides encoding amino acid sequence SEQ ID NO:2 or a DNA

sequence that hybridizes to nucleotides 557-1171 of SEQ ID NO:1 wherein said DNA is at least 70% homologous to nucleotides 557-1171 of SEQ ID NO:1, vectors and host cell comprising the same. The portion of the specification (and the claims) in the reference patent that supports the recited DNA encoding amino acid sequence SEQ ID NO:2 includes several embodiments (variant polynucleotides) that would anticipate the polynucleotides claimed in claims 1-5 and 8-20 herein, in particular the DNA comprising nucleotides 557-1171 of SEQ ID NO:1 and encoding SEQ ID NO:2. Claims of the instant application listed above cannot be considered patentably distinct over claims 1-5 of the reference application when there is specifically recited embodiment that would anticipate claims 1-5 and 8-20 of the instant application. Alternatively, claims 1-5, 8-20 cannot be considered patentably distinct over claims 1-5 of the reference patent when there is specifically disclosed embodiment in the reference patent that supports claims 1-5 of that patent and falls within the scope of claims 1-5, 8-20 herein because it would have been obvious to one having ordinary skill in the art to modify claims 1-5 of the reference by selecting a specifically disclosed embodiment that supports those claims i.e., a variant polynucleotide encoding polypeptide with SEQ ID NO:2 or a sequence that hybridizes to nucleotides 557-1171 of SEQ ID NO:1 that is at least 70% identical to nucleotides 557-1171 of SEQ ID NO:1 and encodes SEQ ID NO:2. One of ordinary skill in the art would have been motivated to do this because that embodiment is disclosed as being a preferred embodiment within claims 1-5 of the reference patent.

This is a provisional rejection because the conflicting claims have not in fact been patented.

In response to previous Office action, applicants have requested that above rejection be held in abeyance. However, as a terminal disclaimer has not yet been filed the above rejection is maintained.

Conclusion

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura

Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.

Manjunath N. Rao
June 5, 2003